TOPIC 02 – Atherosclerosis, haemostasis, inflammation, AGE – B

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0370

Cyclooxygenase pathway activation in sleep apnea syndrome

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Rationale Patients with obstructive sleep apnea syndrome (OSA) exhibit an early vascular remodelling and alterations of acid arachidonic (AA) pathway. Thromboxane A2 (TXA2) is a cyclooxygenase (COX)-derived metabolite of AA involved in vascular remodelling.

Objectives (i) To characterize COX-pathway in apolipoprotein E-deficient (ApoE-/-) mice exposed to chronic intermittent hypoxia (CIH) and in OSA patients in comparison to controls; (ii) To establish the specific role of COX pathway activation in OSA-associated atherogenesis.

Methods 40 male ApoE-/- mice, 14-week-old, were submitted to CIH or normoxia (N) for 8 weeks. Atherosclerosis lesions were determined in aortic roots. Expression of COX-pathway genes were investigated on aortas. 50 lean OSA patients free of known cardiovascular risk factor matched with 25 healthy volunteers (HV) for body mass index and age, were included, as well as 56 OSA patients with cardiovascular co-morbidities. Urinary excretion of 11-dTXB2 was measured by liquid chromatography-tandem mass spectrometry. 116 subjects benefited to carotid ultrasonography to assess intima media thickness (IMT).

Results Exposure of mice to CIH induced an increase of atherosclerotic plaque size in aortic roots (p=0.008). This was associated with an increase of COX-1 (p=0.05) and thromboxane synthase (TXBS) (p=0.03) mRNA levels in aortas. Atherosclerotic plaque size significantly correlated to mRNA levels of COX-1, COX-2, TXBS and prostacyclin synthase. In patients, urinary excretion of 11-dTXB2 did not differ between OSA patients free of cardiovascular complications and healthy volunteers, but was increased in OSA patients with comorbidities compared to OSA patients without (694.0 (425.9-1235.6) *versus* 616.0 (354.3-838.2) pg/mg creatinine respectively; p=0.007). Finally, urinary 11-dTXB2 was increased by 30% in OSA patients with carotid hypertrophy (IMT>0.8mm) compared to OSA patients without carotid hypertrophy (783.0 (582.8-938.0) *versus* 592.9 (278.9-782.5) pg/mg creatinine, respectively; p=0.02).

Conclusion COX-pathway is activated in ApoE-/- mice exposed to CIH and in OSA patients with associated cardiovascular risk factors. This activation seems to be involved in the atherosclerotic process. Therefore, inhibition of COX-pathway could be of potential interest in prevention of cardiovascular morbidity in OSA patients.

0381

Long-term Clinical Outcome after Fractional Flow Reserve-Guided Percutaneous Coronary Revascularization in Patients with Small Vessel Disease

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Background: Small coronary vessels supply small myocardial territories. The clinical significance of small vessel stenoses is therefore questionable. Moreover, percutaneous coronary intervention (PCI) of non-functionally significant lesions does not improve clinical outcome and might even be associated with potential procedural or stent related risks. The aim of this study was to assess the clinical outcome of Fractional Flow Reserve (FFR) guided PCI in the treatment of small coronary vessel lesions as compared with an Angio-guided PCI.

Methods and Results: From January 2004 to December 2008, all patients (pts) treated with PCI for stable or unstable angina in small native coronary vessels (reference vessel diameter and stent size <3mm) were retrospectively analyzed. Pts were divided into an Angio-guided and an FFR-guided PCI group. A total of 717pts were enrolled (495 Angio-guided, 222 FFR-guided). Endpoints were: death, non-fatal myocardial infarction (MI), combined death or non-fatal MI, target vessel revascularization (TVR), and procedure costs. Major adverse cardiac events (MACE) were defined as death, non-fatal MI and TVR.

Clinical follow-up was obtained in 97.5% (median follow-up: 3.3 [from 0.01 to 5] years) of the pts. Seventy-eight pts (35%) had a significant FFR (<0.80) and underwent PCI. Using a propensity score adjusted Cox analysis, pts treated with FFR-guided PCI had significantly lower combined death or non-fatal MI (HR 0.413, 95%CI 0.227-0.750, p=0.004), non-fatal MI (HR 0.063, 95%CI 0.009-0.462, p=0.007), TVR (HR 0.517, 95%CI 0.323-0.826, p=0.006), and MACE (HR 0.458, 95%CI 0.310-0.679, p<0.001). No difference was observed in mortality alone (HR 0.684, 95%CI 0.355-1.316, p=0.255). Procedure costs were also reduced in the FFR guided strategy (3253±102 Euros vs. 4714±37 Euros, p<0.0001).

Conclusions: FFR-guided PCI of small coronary arteries is safe and results in better clinical outcomes when compared to an Angio-guided PCI.

0280

Long-Term Prognostic Value of Pre-Procedural Total Adiponectin Levels in Patients Undergoing Percutaneous Coronary Intervention

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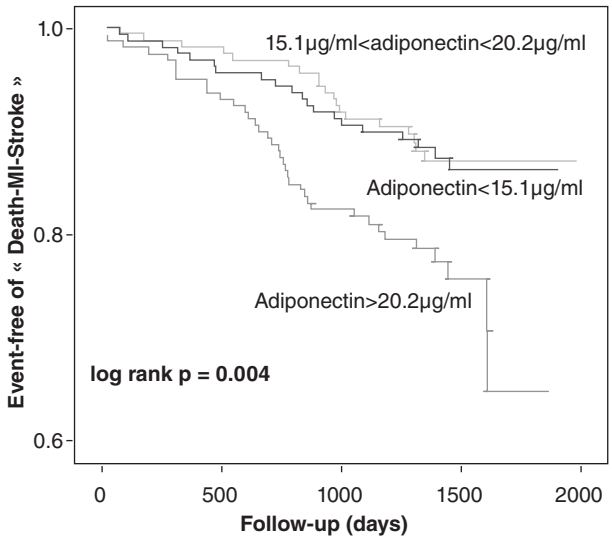
Objective: Adiponectin is considered to possess antiatherogenic and cardioprotective properties. In patients undergoing percutaneous coronary intervention (PCI), the prognostic value of preprocedural total adiponectin is unknown. The present study was designed to address this issue.

Methods: From March 2006 to September 2007, pre-procedural total adiponectin levels were measured in 477 consecutive patients who underwent PCI in our institution with a median follow-up of 3.7 years. Patients presenting with acute ST-elevation myocardial infarction (STEMI) were excluded. The primary endpoint was the composite of death, non-fatal MI or stroke. Target lesion revascularization (TLR) was also examined.

Results: Median adiponectin level was 17µg/ml [25-75th percentile: 13-21µg/ml]. The primary endpoint occurred in 76 patients (15.9%). TLR was undertaken in 25 patients (5.2%). Female gender, high HDL cholesterol and BNP, low triglyceride levels and lack of pre-treatment with beta-blockers were independently associated with high adiponectin level. In univariate analysis, adiponectin had a significant positive relationship (p=0.002) with the primary endpoint. In multivariate analysis, diabetes mellitus, lower creatinine clearance, high CRP and high adiponectin levels (hazard ratio=1.05 [95% CI: 1.01-1.09; p=0.006) were associated with the primary endpoint. When patients were divided into tertiles according to adiponectin levels, patients in the upper tertile (>20.2µg/ml) had twice more risk of death, MI or stroke as compared to patients in the lowest tertile (<15.1µg/ml) (Figure). No association was found between adiponectin levels and TLR (p=0.64).

Conclusions: In contrast to studies in the general population, high preprocedural total adiponectin levels may be associated with increased risk of mortality, MI or stroke in patients undergoing PCI.



KAPLAN-MEIER CURVES FOR SURVIVAL FREE OF DEATH-MI-STROKE ACCORDING TO ADIPONECTIN LEVELS

0054

Deleterious interaction between drug eluting stent implantation and impaired platelet inhibition by clopidogrel following PCI

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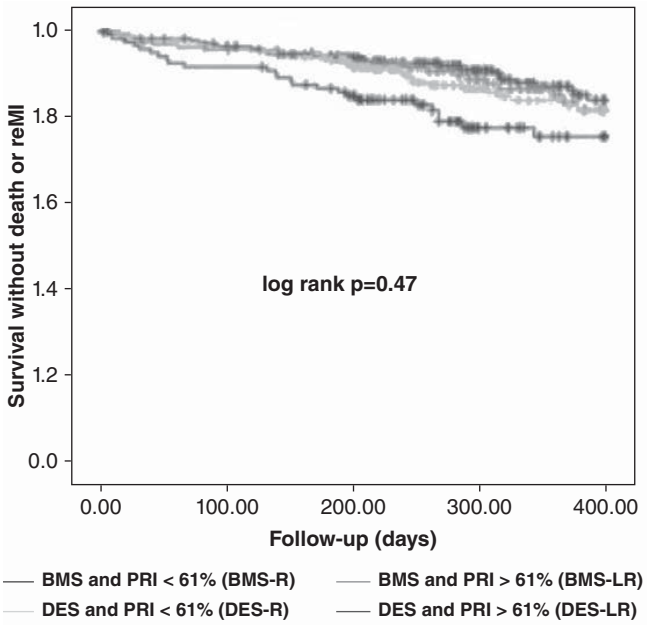
Objectives: To determine whether low platelet response to the $P2Y_{12}$ receptor antagonist clopidogrel as assessed by VAsodilator Stimulated Phosphoprotein flow cytometry test (VASP- FCT) has the same deleterious clinical impact in patients undergoing percutaneous coronary intervention (PCI) and treated with or wihtout drug eluting stent (DES).

Background: Delayed struts reendothelialization following DES implantation together with impaired platelet responsiveness to clopidogrel are likely to promote thrombotic events after PCI. The platelet VASP-FCT assay is specific of the $P2Y_{12}$ ADP receptor-pathway. In this test, platelet activation is expressed as Platelet Reactivity Index (PRI).

Methods: Unselected patients treated by PCI were prospectively enrolled and follow-up for one year. In each sub-group, patients were classified as low-responders (LR: PRI≥61%) and responders (R: PRI<61%) to clopidogrel. The 61% threshold was previously defined as the optimal cut-off value to predict cardiac death following PCI.

Results: 855 patients (64 yr±12) (DES=392; BMS=463) undergoing urgent (n= 648) or planned (n=207) were prospectively enrolled. PRI values were not significantly different in BMS vs DES-treated patients. At a mean follow-up of 282±102 days, cardiac death (BMS-R: 2.1%, BMS-LR 3.7%, DES-R 5.1%, DES-LR 8.5%; p=0.030), death and Re- MI (BMS-R 10.5%, BMS-LR 12.6%, DES-R 12.7%, DES-LR 20.3%; p=0.059), possible stent thrombosis (BMS-R: 0.4%, BMS-LR 1.2%, DES-R 2.7; DES-LR 4.2% p=0.034) rates were higher in DES-LR patients. TVR tend to be lower in DES-R patients (BMS-R: 13.7%, BMS-LR 12.4%, DES-R 6.8%, DES-LR 9.5%; p=0.063). Conversely, in BMS treated patients, LR was not associated with poorer cardiovascular outcome.

Conclusions: Interaction between impaired platelet responsiveness to clopidogrel and DES implantation is a strong predictor of adverse cardiovascular outcome at one year following PCI.



Death and myocardial infarction at follow-up

0309

Predictive value of renal function degradation before coronary artery bypass surgery

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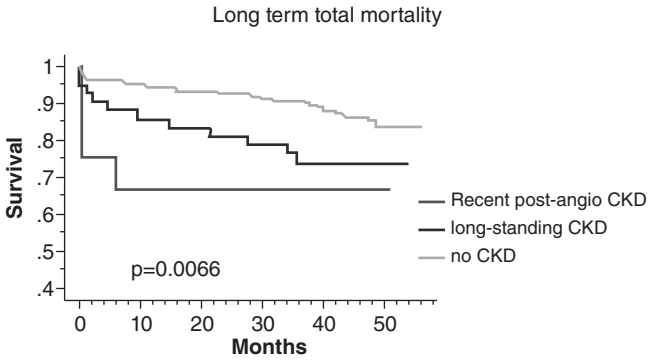
Objective. Patients with advanced age and comorbidities are increasingly referred for cardiac surgery. Chronic kidney disease (CKD) is a marker of poorer post-operative prognosis and is included in peri-operative risk scores. However, it is not clear whether recent renal failure occurring after coronary angiography has similar prognostic value than long-term CKD. The purpose of our study was to compare the prognostic value of recent vs. long-standing CKD in patients undergoing CABG.

Methods. We prospectively studied 383 patients undergoing CABG in a single center. Demographic and clinical data were collected preoperatively. The glomerular filtration rate (GFR) was evaluated before surgery and coronary angiography according to the MDRD-equation. We defined CKD when GFR < 60ml/min/1.73m². Patients were categorized into 3 groups (group 1: no CKD prior to surgery; group 2: CKD before coronary angiography and surgery; group 3: no-CKD before coronary angiography, but CKD before surgery). Multivariate Cox proportional hazard analysis was performed to determine the independent prognostic factors. The primary outcome was long-term total mortality. The secondary outcome was composite, combining long-term death, acute coronary syndrome, stroke and coronary revascularization.

Results. During a median follow-up of 39±14 months, poorer prognosis was observed in groups 2 and 3 vs. group 1 (figure 1). In the multivariate analysis adjusting for confounders, we found an increased risk of mortality (hazard ratio (HR) and 95% confidence interval: 3.9 [1.1-13.5]; p=0.03) and secondary outcome (HR: 3.7 [1.1-12.8]; p=0.04) in group 3 compared to group 1, but no significant risk was found in group 2 (mortality: HR 1.1 [0.5-2.4]; p=0.79).

Conclusions. Recent preoperative renal dysfunction occuring between coronary angiography and surgery is an independent predictor of long-term mortality.

KEYWORDS: Coronary artery bypass; Coronary angiography; Kidney Disease; Prognosis; Predictive Factors.



long-term mortality

0383

Five-Year Clinical Outcome in Elderly Population with Small Vessel Disease Treated with Drug-Eluting *Versus* Bare-Metal Stenting

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Background: Drug-eluting stents (DES) are more effective than bare-metal stents (BMS) in the treatment of small coronary vessel lesion. There are limited data on the safety and efficacy of DES in this indication in elderly patients. We aimed to assess the long-term clinical outcome in elderly patients of DES vs. BMS in small vessel disease.

Methods: From January 2004 to December 2008, all elderly patients (≥75 years) treated with stenting of native small coronary arteries (defined as reference vessel diameter and implanted stent < 3mm) were prospectively enrolled. According to the type of stent implanted, patients were divided into BMS and DES group. Procedural and long-term clinical outcomes were compared between both groups.

Results: A total of 293 patients were enrolled (175 treated with BMS, 118 with DES). Clinical follow up was obtained in 96.2% (median follow-up 3.7±1.4 years). At five years, patients treated with DES showed significantly lower major adverse cardiac events (MACE) (HR 0.42, 95% CI 0.24-0.72, log-rank P=0.002) and target vessel revascularization (TVR) (HR 0.33, 95% CI 0.14-0.76, log-rank P=0.009). No significant differences were observed between the two groups as to death, myocardial infarction and stent thrombosis.

Conclusion: In this real-world registry of small vessel disease, DES was safe and more effective than BMS in reducing MACE and TVR at 5 years in elderly patients.

0386

Potential clinical benefit of final kissing inflation after single stenting for the treatment of bifurcation coronary lesions

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Purpose: The aim of this study was to evaluate clinical benefit in bifurcation lesions treated with provisonnel stenting strategy and final kissing inflation as compared with non-final kissing inflation.

Methods: From February 2004 to June 2010, 103 patients with all types of Medina bifurcation lesions were enrolled in a prospective study. All patients underwent implantation of a stent across the bifurcation and provisional SB stenting. 45 (43%) patients were assigned to treatment with final kissing balloon inflation (FKI group), the others were treated with isolated balloon after dilation (n=57, non-FKI group).

Results: No significant differences were found between the patients from the FKI and non-FKI groups in terms of age, risk factors, clinical status, or location of the bifurcation lesions. During 24 months fellow up, eight patients experienced a Q-wave acute myocardial infarction: four (7.5%) from the non FKI group and four (9%) from the non-KB group. Target lesion revascularization was required in 13 patients (12%): 7 from the FKI group and 6 from the non-FKI group. Late mortality occurred in 1 patient from the FKI group and 1 patient from the non-FKI group. Definite stent thrombosis occurs in eight cases (7%): 5 from the FKI group and 3 from the non-FKI (p=NS). The incidence of major events at 2 year (death, target lesion revascularization, or acute myocardial infarction) was similar in both groups: 11 (31%) from the FKI group and 16 (28%) from the non-KB group (p=NS).

Conclusion: no differences in the clinical outcome at 2 year of follow-up were observed between the patients with bifurcation lesions treated with a simple approach and either a simultaneous final KB or an isolated SB balloon post-dilation.

0306

Identification of coagulase negative staphylococci in human pathology: comparison of different identification methods

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Background: coagulase-negative staphylococci (CNS) are part of the normal skin flora, but can also emerge as opportunistic pathogens like in endocarditis. Therefore, to define the clinical significance of these bacteria, it has become increasingly important to accurately identify the CNS to species level. Several phenotypic and genotypic methods are available. Mass spectrometry is a recent technic wich has not yet been compared to traditional methods in CNS identification.

Method: we prospectively collected 218 CNS on blood cultures. We assessed the identification performance of three phenotypic tests (API ID 32 staph, TAXIden Staph, Vitek system), and MALDI-TOF spectrometry, compared to genotypic identification, based on the sequence analysis of the rpoB gene, which is considered as the identification reference method.

Results: Genotypic methods have better typeability and accuracy than phenotypic one but tend to be more expensive and time-consuming. This study provides evidence of the validity and usefulness of MALDI-TOF Mass Spectrometry which appears to have a higher discriminatory power than other phenotypic methods, and an excellent correlation with genotypic identification. Indeed, correct species was obtained in 93% and only 13 isolates were misidentified.

Conclusion: in this study, we demonstrate that MALDI-TOF Mass Spectrometry is a powerful tool for the identification of clinically relevant species of CNS, and a promising technique that enables construction of elaborate databases. It provides a rapid and inexpensive tool for bacterial identification by extending this strategy to other groups of pathogenic bacteria in routine clinical microbiology laboratories.